

ANODIC SUBSTITUTION; ACYLOXYLATION AND ALKOXYLATION

av
Zoltan Blum

Lund 1981



Digitized by the Internet Archive
in 2026

https://archive.org/details/IA41553201_0035

ANODIC SUBSTITUTION;
ACYLOXYLATION AND ALKOXYLATION

av

Zoltan Blum, fil. kand., Sm.

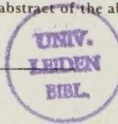
Lund 1981

Organization LUND UNIVERSITY	Document name DOCTORAL DISSERTATION	
Chemical Center	Date of issue December 1981	
	CODEN: LUNK DL/(NKOK-1002)/1-34(1981)	
Author(s) Zoltan Blum	Sponsoring organization	
Title and subtitle ANODIC SUBSTITUTION; ACYLOXYLATION AND ALKOXYLATION		
Abstract Determination of the <u>nuclear to side-chain acetoxylation ratio of triptycene</u> and <u>fluorene</u> and a discussion of the results based on structural features have been presented. Anodic trifluoroacetoxylation of benzene and deactivated benzenes and <u>synthesis of perfluorinated quinones</u> by means of anodic oxidation of perfluoro arenes in trifluoroacetic acid have been demonstrated. The mechanism of anodic alkoxylation of <u>N,N-disubstituted carboxamides</u> has been investigated. Thus, the possibility of <u>substitution of the formyl hydrogen in N-α peralkylated formamides</u> on anodic oxidation was demonstrated. <u>N-Acetylaziridine</u> and <u>N-formylazetidine</u> were <u>oxidized anodically</u> in methanol. No normal methoxylated amides were formed, the absence of which substantiated the limit in <u>N-α methoxylation of N-acylheterocyclic amides</u>. Five <u>N,N-dimethyl-ω-hydroxyalkyl carboxamides</u> were <u>oxidized anodically</u> in various solvents. No products derived from cyclization were detected when electrolyses were performed in inert solvents. On oxidation in methanol, <u>N-α methoxylated products</u> were isolated, the cyclization of which to <u>N-methyl-4-oxo-1,3-oxazaheterocycles</u> were accomplished by acid catalysis in homogeneous solution.		
Key words		
Classification system and/or index terms (if any)		
Supplementary bibliographical information		Language English
ISSN and key title		ISBN
Recipient's notes	Number of pages	Price
	Security classification	

Distribution by (name and address) Organic Chemistry 3, Chemical Center, University of Lund, P.O. Box 740, S-220 07 Lund 7, Sweden

I, the undersigned, being the copyright owner of the abstract of the above-mentioned dissertation, hereby grant to all reference sources permission to publish and disseminate the abstract of the above-mentioned dissertation.

Signature _____



Date November 10, 1981

Señor, Señor, do you know where we're headin'
Lincoln County Road or Armageddon
Seems like I've been down this way before
Is there any truth in that, Señor

- - -

Well, the last thing I remember before I stripped and kneeled
Was that trainload of fools bogged down in a magnetic field
A gypsy with a broken flag and a flashing ring
Said, "Son this ain't a dream no more, it's the real thing"

- - -

Señor, Señor, let's disconnect these cables
Overturn these tables
This place don't make sense to me no more
Can you tell me what we're waiting for, Señor

Bob Dylan

This review summarizes results from the following papers which will be referred to by the Roman numerals I-VI.

- I. Z. Blum, L. Cedheim and L. Ebersson
Studies on Anodic Substitution Reactions. XI. The Anodic Oxidation of Triptycene and Fluorene and Its Implications for the Side-chain Mechanism.
Acta Chem. Scand. B 31 (1977) 662.
- II. Z. Blum, L. Cedheim and K. Nyberg
Studies on Anodic Substitution Reactions. X. Anodic Tri-fluoroacetoxylation of Benzene and Deactivated Benzenes.
Acta Chem. Scand. B 29 (1975) 715.
- III. Z. Blum and K. Nyberg
Anodic Synthesis of Fluorinated Quinones.
Acta Chem. Scand. B 33 (1979) 73.
- IV. Z. Blum, M. Malmberg and K. Nyberg
Studies on Anodic Substitution Reactions. XVIII. Attempted Methoxylation of N-Acetylaziridine and N-Formylazetidine.
Acta Chem. Scand. In press.
- V. Z. Blum and K. Nyberg
Studies on Anodic Substitution Reactions. XIX. Anodic Oxidation of N,N-di-tert-Butylformamide and N-Formyl-2,2,6,6-tetramethylpiperidine.
Acta Chem. Scand. In press.
- VI. Z. Blum and K. Nyberg
Studies on Anodic Substitution Reactions. XXI. Anodic Oxidation of N,N-Dimethyl- ω -hydroxyamides.
Acta Chem. Scand. In press.

CONTENTS

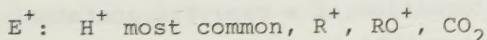
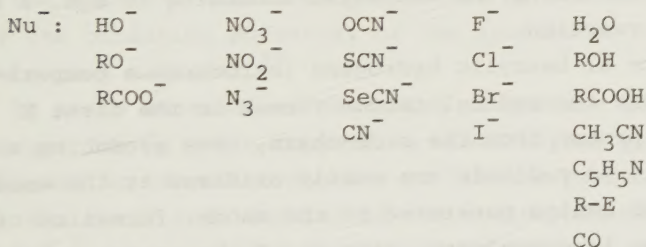
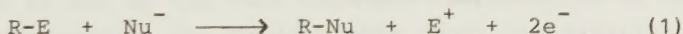
1.	INTRODUCTION	7
1.1	General aspects	7
1.2	Acetoxylation	8
1.3	Trifluoroacetoxylation	9
1.4	Alkoxylation	10
2.	ACYLOXYLATION OF AROMATICS	12
2.1	Nuclear <u>versus</u> side-chain acetoxylation	12
2.2	Trifluoroacetoxylation of substituted benzenes	14
2.3	Synthesis of perfluorinated quinones	18
3.	METHOXYLATION OF N,N-DISUBSTITUTED CARBOXAMIDES	21
3.1	General aspects	21
3.2	Anodic oxidation of <u>N</u> -acetylaziridine and <u>N</u> -formyl-azetidine	23
3.3	Anodic oxidation of <u>N,N</u> -di- <u>tert</u> -butylformamide and <u>N</u> -formyl-2,2,6,6-tetramethylpiperidine	24
3.4	Methoxylation of ω -hydroxyalkyl- <u>N,N</u> -dimethyl-carboxamides	25
4.	REFERENCES	32

1. INTRODUCTION

1.1 General aspects

Organic electrochemistry, among organic chemists regarded as a somewhat obscure if not to say bizarre area of research is nevertheless gaining recognition as a practicable and powerful vehicle for organic synthesis. During the past twenty years a large number of workers have devoted their efforts to expand this field of research. As in any expanding field the demand for an adequate theoretical model was strong and initiated numerous mechanistic studies. This resulted in a throng of papers and reports concerning synthetic applications and their mechanistic interpretation. The last decades' condensation and systematization of previous findings have rendered the field somewhat less pragmatic so that our present body of knowledge enables us to explain and interpret encountered phenomena in a reasonably satisfactory way.¹⁻¹⁰

Among the many applications of organic electrochemistry is anodic substitution,¹¹ i.e. the replacement of a hydrogen (or another suitable group) with a chosen nucleophile. Activation by electron-rich groups facilitates the reaction but is not compulsory and nucleophiles can be found among species usually used as such¹² (eqn. 1).

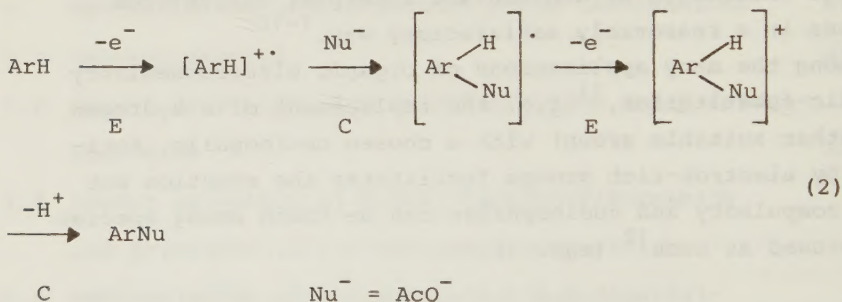


Since the only restriction is the difference in oxidation

potential between the reactants this method has a high synthetic potential. As the reaction involves "Umpolung", *i.e.* nucleophilic substitution on what is formally a nucleophilic precursor, otherwise inaccessible reactions can be realized.¹² Sometimes it is also possible to prepare unique compounds.

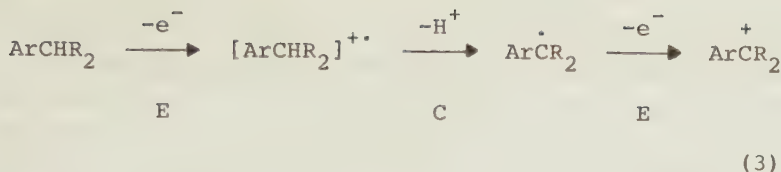
1.2 Acetoxylation

The formation of aryl acetates via electrolysis of aromatic compounds in acetic acid/sodium or potassium acetate is a well documented and thoroughly examined reaction.¹³ The direct mechanism as suggested by Ebersson in 1963 features the stepwise removal of two electrons from the aromatic nucleus, E steps, interjected by chemical, C steps where the nucleophile attacks the radical cation initially formed and where a proton is removed by a base present (eqn. 2).¹⁴



Thus a reaction following the mechanism according to eqn. 2 is denoted an ECEC reaction.

The presence of benzylic hydrogens introduces a competitive element where the radical cation formed in the first E step can lose a proton from the side-chain, thus producing a benzylic radical. As radicals are easily oxidized at the anode or by the radical cation generated at the anode, formation of a benzylic cation is compulsory. Capture of the cation by the nucleophile results in the formation of a benzylic acetate (eqn. 3). A molecule possessing both kinds of hydrogen atom usually displays substitution in the side-chain (α) as well as in the aromatic nucleus.¹⁵ The nuclear to α substitution ratio



C



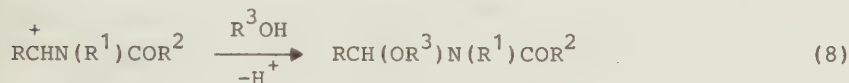
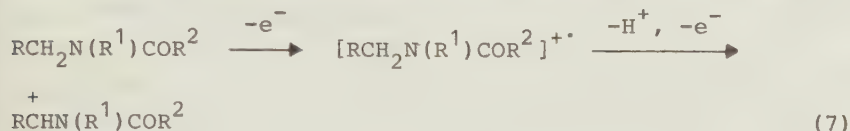
is governed either by factors hidden in structural features or,¹⁵ as has been shown recently, can be influenced by the subsequent rearrangement of initially formed addition compounds.¹⁶

1.3 Trifluoroacetoxylation

The versatility of the acetic acid/acetate system is limited by the discharge potential of acetate ion, at and above which the formation of carbon dioxide and methyl radicals is predominant. In order to obtain the desired acetoxylation products the utilization of aromatics with a sufficiently low oxidation potential is essential.¹⁷ This property is prevalent in aromatics possessing electron-releasing substituents. Another limit is set by the fact that the introduction of an acetoxy group renders the product more prone to oxidation, i.e. the electron-releasing properties of the acetoxy group lower the oxidation potential of the product as compared to the starting material.¹⁸

To avoid concomitant oxidation of acetate ion, it was exchanged for an inert supporting electrolyte, e.g. a tetraalkylammonium tetrafluoroborate or lithium perchlorate. However, the resulting lowering of the nucleophilicity, acetic acid being substantially less nucleophilic than acetate ion, entailed exclusive side-chain substitution^{17,19} and/or the formation of coupling products²⁰ (dehydrodimers; two mechanistic alternatives are shown in eqns. 4 and 5).

Ordinary preparative procedures for the essential $\underline{N}$ - α oxygenated tertiary amides include mainly the reduction of imides and are thus structurally limited.²² Anodic oxidation of the parent amides in the presence of alcohols offers an easy and convenient route to $\underline{N}$ - α alkoxyated derivatives. The method is adaptable to a vast number of amides producing the desired alkoxyated compounds in excellent yields (eqns. 7 and 8).²³



Compared to the high level of complexity usually associated with modern synthetic achievements electroorganic synthesis is regularly relatively simple. Thus the anodic alkoxylation of amides involves use of inexpensive and easily accessible starting materials in combination with the simplest possible type of electrolysis equipment. Reaction conditions are percussively insensitive to extraneous factors and workup is confined to a simple distillation.^{23b}

The reaction mechanism is believed to be of the general type postulated for anodic substitution: Formation of a radical cation via one-electron transfer from the amide linkage followed by deprotonation and subsequent oxidation of the intermediate radical (eqn. 7). The acylimmonium ion so formed is then scavenged by the solvent/nucleophile (eqn. 8).

Limitations can be found in the oxidation potential of the solvent/supporting electrolyte system, above which formaldehyde formation from the usually employed solvent methanol is predominant. This is seldom a problem when tertiary amides are used but must be taken into account when dealing with secondary amides, these compounds being substantially more difficult to oxidize.²⁴

2. ACYLOXYLATION OF AROMATICS

2.1 Nuclear versus side-chain acetoxylation

The phenomenon of concomitant nuclear and side-chain (α) acetoxylation when benzylic hydrogens are present was recognized early in the studies of anodic acetoxylation of aromatics.²⁵ A lot of effort was made to explain and enable the prediction of the nuclear to α substitution ratio.²⁶ Being a common feature of oxidative substitution processes promoted by such different oxidants as the anode, metal ions²⁷ and peroxydisulfate²⁸ it was used to illustrate differences or similarities in mechanistic interpretations. It was soon understood that the outcome of a reaction was determined by stabilizing/destabilizing factors in the molecule examined.¹² Any structural feature with the ability to favour a certain reaction path would strongly influence the nuclear to α substitution ratio.

Albeit in different ways, triptycene (Tr-H, Fig. 1) and fluorene (Fl-H, Fig. 2) represent limiting structures in anodic side-chain substitution. Tr-H, being in essence a bicyclic



Fig. 1

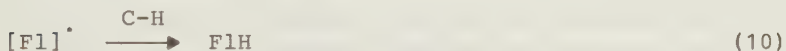
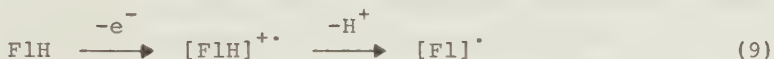


Fig. 2

system, would have to tolerate the formation of a bridgehead radical in order to follow the mechanism of eqn. 3. As the radical so formed would considerably deviate from planarity one would anticipate a high nuclear to α substitution ratio relative to structurally similar compounds, e.g. triphenylmethane. This would stress the validity of the first C step of eqn. 3 where the entering nucleophile either could act as a base, forming the radical, or attack the aromatic nucleus, i.e. the energetically favoured path will be chosen. On the

other hand Fl-H would not show any resistance towards forming $[Fl]^+$, the limiting process being the formation of the cation after the removal of the second electron (eqn. 3, second E step). The fluorenyl cation so formed is formally antiaromatic and its formation should have a detrimental effect on the reaction course. Compared to the analogous diphenylmethane Fl-H should display a higher nuclear to α substitution ratio. Paper I clearly demonstrates the validity of these predictions. A nuclear to α substitution ratio of 250 for triptycene as compared to the value of 0.17 found for triphenylmethane is indicative of inhibitive factors for α substitution present within the molecule. Also the difference in the values found for fluorene and diphenylmethane, 35 and 4.3, respectively, clearly suggests that nuclear substitution is favoured owing to structural features exhibited by the fluorene molecule.

Considering the results obtained for compounds structurally related to fluorene the rather low yield of acetoxylated products constituted an anomaly. In order to rationalize this phenomenon a substrate regenerating process was suggested (eqns. 9 and 10). This suggestion has been subjected to further



examination, in that the fate of 9,9'-bisdeuterium-labelled fluorene upon electrolysis was studied.²⁹ These results clearly indicate that the intervention of a regenerating process as proposed in Paper I is improbable. An explanation as to why the current yield in fluorene acetoxylation is unusually low is yet to be found.

Both Tr-H and Fl-H possess structural features that are predicted to increase the nuclear to α substitution ratio. Any molecule with properties capable of stabilizing an intermediate benzylic cation should behave oppositely, *i.e.* the nuclear to α substitution ratio should be lower than that displayed by structurally analogous compounds. 5H-Dibenzo[a,d]cycloheptene, capable of forming a highly stabilized dibenzotropylium ion³⁰

upon oxidation (eqn. 3, second E step) seemed to be the molecule of choice in order to verify this assumption (Fig. 3).

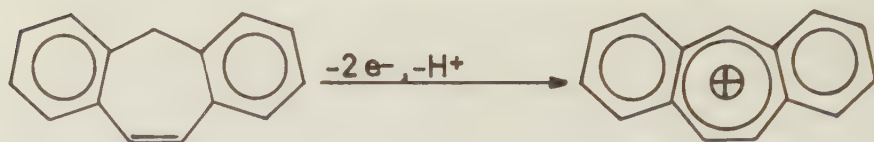


Fig. 3

Surprisingly, anodic oxidation in acetic acid/acetate revealed an almost complete inertness towards these reaction conditions leading to nearly quantitative substrate recovery. Utilization of acetic acid/tetrabutylammonium tetrafluoroborate, a system known to promote exclusive side-chain acetoxylation, did not alter the outcome of the reaction. In an attempt to find a rationale the expected product, 5-acetoxy-5H-dibenzo[a,d]-cycloheptene, was co-electrolyzed with the starting material and it was discovered that the former did not endure the electrolysis conditions. Nevertheless, the instability of the expected product does not explain why the starting material survives during electrolysis.³¹ A possible explanation might be that if a dibenzotropylium ion is formed it might be stable enough to reach the cathode where it could be reduced, thus regenerating the starting material. This assumption, however, remains to be proved.

2.2 Trifluoroacetoxylation of substituted benzenes

As discussed in the introduction the use of the acetic acid/alkali metal acetate solvent/supporting electrolyte system suffers from certain disadvantages. The relatively low discharge potential of acetate ion makes it impracticable to obtain acetoxylation products from deactivated aromatics.³² Even benzene itself fails to be acetoxylated in the acetic acid/acetate system, yielding only minute amounts of phenyl acetate.^{25a} The successful use of trifluoroacetic acid in the

oxidation of aliphatic hydrocarbons and the known cation-stabilizing effect of strong acids was suggestive of its usefulness as oxidation medium.³³ Moreover, properties such as high conductivity, high solubility for most organic compounds and low boiling point supported the issue. It was considered that drawbacks such as high toxicity and a pronounced tendency to take up atmospheric moisture were able to be controlled. Platinum proved to be the anode material of choice since the use of graphite resulted in fast anode degradation. As the intended substrates were more or less deactivated aromatics and thus prone to cathodic reduction it seemed necessary to introduce a cell divider.

Paper II presents the result obtained from anodic trifluoroacetoxylation of a number of deactivated aromatic compounds. It is essential to underline that the aim of Paper II was to illustrate the versatility and scope of the method. No effort was taken to optimize the yields or to influence the isomer distribution (Table 1).

Table 1. Anodic trifluoroacetoxylation of aromatic compounds. Product yields and isomer distribution (observed and calculated).

X in PhX	Isomer distribution						Current yield (%)
	Observed			Calculated			
	<u>o</u>	<u>m</u>	<u>p</u>	<u>o</u>	<u>m</u>	<u>p</u>	
H							27
COOCH ₃	51	34	15	54	16	30	65
NO ₂	22	59	19	30	43	27	60
CF ₃	35	47	18	50	35	15	31
COOCH ₃	54	32	14	52	17	31	67
COPh	70	18	12	54	15	31	21
CN	45	30	25	42	30	28	10

Aryl trifluoroacetates were formed in all instances although the yields varied. The trifluoroacetates thus produced were easily hydrolyzed to the corresponding phenols and the procedure constitutes a synthetic route towards oxygen-containing deactivated aromatics.

In the anodic acetoxylation of substituted benzenes, the presence of an electron-releasing group usually gives an isomer distribution closely resembling the pattern observed in electrophilic aromatic substitution. By analogy one would then assume that an electron-attracting substituent would cause predominant meta substitution. As can be seen from Table 1 this was not the case. Instead a fair correlation with substitution patterns based on charge distribution, as calculated by the INDO method, was obtained. These results are indicative of a reaction mechanism where the entering nucleophile attacks at the position of highest positive charge density in the radical cation.

Interesting comparisons can be made from the results cited here and isomer distributions reported elsewhere. Thus Miller et al. in two papers³⁴ account for the fate of some deactivated aromatics on anodic oxidation in 2:1 dichloromethane/trifluoroacetic acid and 2:1 nitromethane/trifluoroacetic acid, respectively. Acetophenone when oxidized in the former solvent mixture, tetraethylammonium tetrafluoroborate being the supporting electrolyte, furnishes predominant ortho substitution (the authors comment on the possible presence of the para isomer, the amount of which was, however, not determined). Analogous treatment of ethyl benzoate provides a 70/30 ortho/para ratio with no formation of the meta derivative. On the other hand, when these compounds are oxidized in the latter solvent mixture utilizing sodium trifluoroacetate as supporting electrolyte all of the three possible isomers are formed, distributed in agreement with the findings in this work. The authors do not comment on this discrepancy but the results might be interpreted in terms of lowered nucleophilicity in the dichloromethane/trifluoroacetic acid system due to the use of an inert supporting electrolyte. Weinberg and Wu, in a contemporary report,³⁵ present results from oxidation of nitrobenzene and benzonitrile under conditions almost equivalent to this

work. For the former there is a percussive concordance between the two sets of isomer distributions but for benzotrifluoride the agreement is poor. The absence of the meta isomer and the reported use of a low-performance SE-30 GLC column indicate that the authors might not have been able to separate the meta and para trifluoroacetates/phenols, a problem often encountered in the preparation of this work. Finally two overlapping reports from Fritz *et al.*³⁶ and Miller *et al.*,^{34b} respectively, are worth commenting on. Both papers are concerned with the trifluoroacetoxylation of chlorobenzene, a compound not included in paper II but where the isomer distribution was determined in this laboratory by the method related here.³⁷ The findings of Fritz agree well with the results obtained in this laboratory, whereas Miller arrives at an entirely different product composition. Once again the meta isomer is absent and when recognizing the difficulties involved in the separation of the meta and para isomers of chlorophenol (separation by GLC is not feasible when using non-capillary columns) an explanation of the discrepancy in terms of a separation problem seems pertinent. The facts and figures discussed above are summarized in Table 2.

In order to investigate the fate of activated aromatics in the trifluoroacetic acid/trifluoroacetate system and thus gain information valuable for comparison with acetoxylation, a selection of substrates commonly employed in acetoxylation was examined. Electrolysis of toluene, naphthalene, biphenyl and anisole respectively, in trifluoroacetic acid, led, however, to complete substrate disintegration.³¹ Probably the high stability, in this medium, of the intermediate cationic species offers an opportunity for weaker nucleophiles than trifluoroacetate ion to interact. Fritz and Kremer, employing the unorthodox solvent mixture acetone/trifluoroacetic acid, 15:1, with sodium trifluoroacetate as supporting electrolyte, were able to prepare aryl trifluoroacetates and their phenolic hydrolysis products from a number of alkylbenzenes.³⁸

Table 2. Anodic trifluoroacetoxylation of monosubstituted benzenes PhX.

X in PhX	Isomer distribution			Ref.
	<u>o</u>	<u>m</u>	<u>p</u>	
CH ₃ CO	54	32	14	a
CH ₃ CO ^b	100	—	— ^h	34a
CH ₃ CO ^c	63	17	20	34b
R'OCO	51	34	15	a
R'OCO ^b	70	—	30	34a
R'OCO ^c	61	17	22	34b
NO ₂	22	59	19	a
NO ₂ ^d	32	54	14	35
CF ₃	35	47	18	a
CF ₃ ^e	28	—	72	35
Cl ^f	33	5	62	37
Cl ^c	15	— ^h	85	34b
Cl ^g	41	3	56	36

^a This work. ^b In CH₂Cl₂-CF₃COOH (2:1), 0.1 M Et₄NBF₄.

^c In CH₃NO₂-CF₃COOH (2:1), 0.67 M NaOCOCF₃. ^d 0.5 M in

C₆H₅NO₂. ^e Undivided cell. ^f Conditions identical to this work. ^g At 2F mol⁻¹. ^h Not determined.

2.3 Synthesis of perfluorinated quinones

At the time of preparation of the work summarized in paper II a remarkable finding was reported from this laboratory. 2- or 4-Fluoroanisole when oxidized in acetic acid/acetate medium did not form the expected acetoxyated compounds (acetoxyfluoroanisoles) but instead the formation of 2- or 4-ace-

toxyanisole was observed.³⁹ Being formally unoxidized derivatives of the starting materials, seemingly the outcome of nucleophilic aromatic substitution, their formation evaded any reasonable explanation at the time (recent reports from Ebersson and Jönsson revealed the participation of "hole" catalysis, indicative of an $S_{ON}2$ mechanism).⁴⁰ Other monofluorinated benzenes did not show any similarity in that fluorine substitution was not feasible.³⁹ It thus seemed worthwhile to examine the fate of perfluorinated arenes upon oxidation, where the absence of hydrogen atoms ultimately would have to result in fluorine substitution or addition to the aromatic ring. This approach proved fruitful and provided a new synthetic route to fluorinated quinones. Upon oxidation in trifluoroacetic acid/potassium trifluoroacetate and subsequent hydrolysis hexafluorobenzene and octafluoronaphthalene were converted to tetrafluorobenzoquinone and hexafluoronaphthoquinone, respectively. Yields were in the range of 60-75 % and the ease of preparation makes the method competitive with other methods available. An attempt to prepare the analogous octafluorobiphenylquinone from decafluorobiphenyl furnished a mixture of quinonoid derivatives (Paper III).

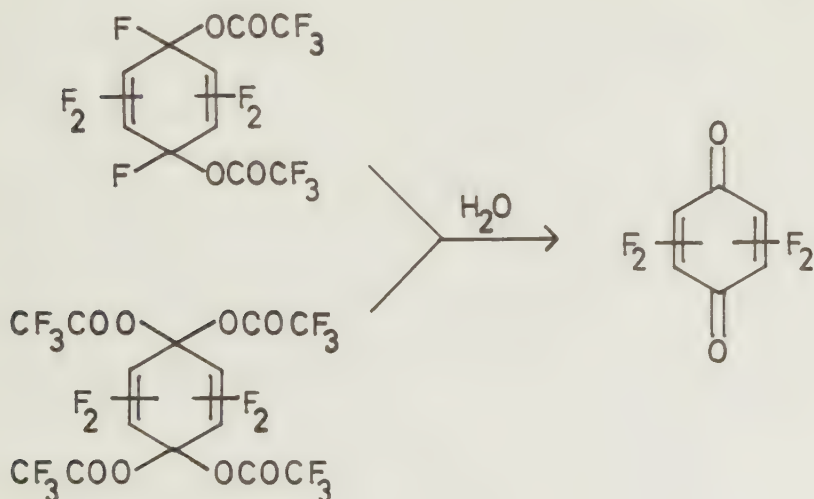


Fig. 4

No attempt was made to study the underlying mechanism but one can speculate on the intermediacy of ketals/mixed ketals. The formation of hydrolyzable intermediates is requisite since the characteristic intense colour of the quinones does not appear during electrolysis but only after the addition of water to the electrolyte (Fig. 4).

In an effort to extend the scope of the reaction to the preparation of quinones other than fluorinated ones, hexachlorobenzene and hexbromobenzene were oxidized in the manner adopted for the fluorinated compounds. Unfortunately, both these compounds proved to be inert to the reaction conditions,³¹ the only reaction being the discharge of trifluoroacetate ion (eqn. 11).



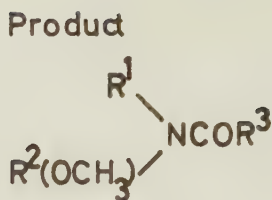
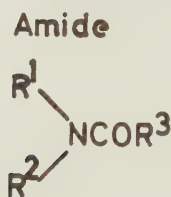
3. METHOXYLATION OF N,N-DISUBSTITUTED CARBOXAMIDES

3.1 General aspects

Capitalizing on the large body of knowledge drawn together by workers in the field of amine oxidation it was soon realized that its gross features were applicable to amides as well.⁴¹ The main distinction between amine and amide oxidative chemistry is the substantially higher oxidation potentials²⁴ for the latter owing to the electron-attracting properties of the acyl group. This might be regarded as an obstacle but is in fact an advantage since the moderating effect of the acyl group influences the reactivity of the intermediates, keeping unwanted side-reactions which usually make amine oxidations impracticable, to a minimum.

The methodology follows the general electrochemical approach: The amide is oxidized in a medium utilized as both solvent and nucleophile, usually methanol or any of the lower alcohols. Sufficient conductivity is provided by the addition of a suitable supporting electrolyte, tetraalkylammonium tetrafluoroborates being commonly employed. Reactions are conveniently run in single-compartment electrochemical cells,⁴² and there is seldom need for the use of elaborate cell-dividers or/and controlled potential operation.²³ As indicated above the reaction is clean and contaminants possibly present are probably formed during the work-up procedure. Table 3 displays a selection of successful methoxylations where the high yields and the variety in amide precursors can be noted. Other alcohols than methanol can be used but yields decrease with increasing chain length.^{23d} The scope of the method is further extended by the use of carbamates as precursors. Alkoxylation proceeds as smoothly as in the amide cases, thus producing N- α alkoxyated carbamates in high yields.⁴³

Table 3. Methoxylation of amides.

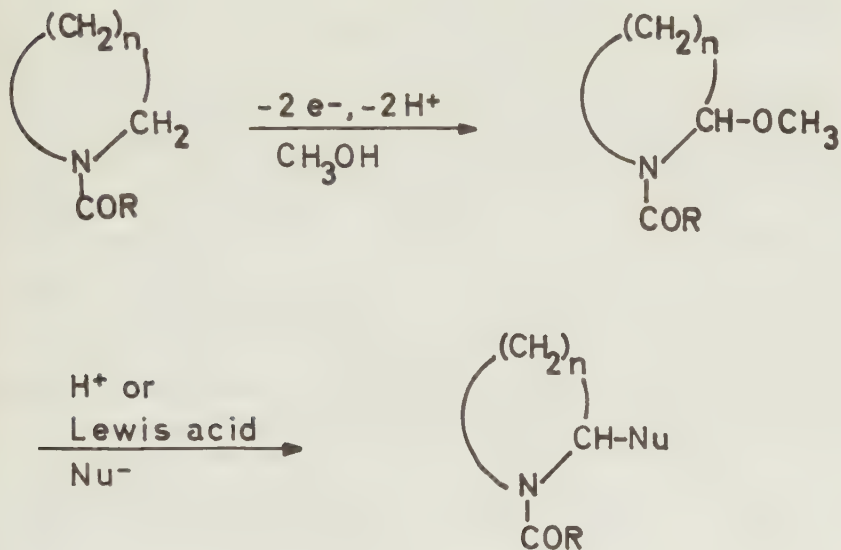


R ¹	R ²	R ³	Yield ^a (%)	Ref.
CH ₃	CH ₃	H	100	23a
CH ₃	CH ₃	CH ₃	78 ^b	23a
CH ₃	CH ₃	C ₆ H ₅ CH ₂	85	23c
C ₂ H ₅	C ₂ H ₅	H	89	23b
C ₂ H ₅	C ₂ H ₅	CH ₃	84	23b
C ₂ H ₅	C ₂ H ₅	C ₆ H ₅	76	23c
<u>i</u> -C ₃ H ₇	<u>i</u> -C ₃ H ₇	H	24	23b
-C(CH ₃) ₂ CH ₂ CH ₂ -		H	50	23d
-(CH ₂) ₄ -		H	97	23b
-(CH ₂) ₄ -		CH ₃	85	23d
-(CH ₂) ₄ -		C ₆ H ₅	62	23c
-(CH ₂) ₅ -		H	95	23b
-(CH ₂) ₅ -		CH ₃	73	23d
-(CH ₂) ₅ -		CF ₃	80	23d
-(CH ₂) ₅ -		C ₆ H ₅	85	23c
-(CH ₂) ₅ -		2F-C ₆ H ₄	85	23d
-(CH ₂) ₅ -		3CH ₃ O-C ₆ H ₄	48	23d
-(CH ₂) ₆ -		H	96	23b
-(CH ₂) ₆ -		CH ₃	95	23d
-(CH ₂) ₂ -O-(CH ₂) ₂ -		H	92	23a
-(CH ₂) ₂ -N(CHO)-(CH ₂) ₂ -		H	91	23a
-CH(CH ₃)(CH ₂) ₃ CH(CH ₃)-		CH ₃	63	23d

^a Isolated.^b n-Butoxylation.

3.2 Anodic oxidation of N-acetylaziridine and N-formylazetidine

After initial studies of open-chain N,N-disubstituted amides efforts were concentrated on the examination of heterocyclic N-acyl compounds. Thus the successful N- α methoxylation of seven-, six- and five-membered N-acylheterocyclic compounds was achieved.^{23b} These compounds were forthwith recognized as useful and remunerative synthetic intermediates⁴⁴ (Fig. 5, $n = 3, 4, 5$).



$n=1,2,3,4,5$

Fig. 5

As an obvious consequence of these findings a thorough survey of the four- and three-membered analogues was undertaken (Fig. 5, $n = 1, 2$). Unfortunately, neither N-formylazetidine (Fig. 5, $n = 2$) nor N-acetylaziridine (Fig. 5, $n = 1$) behaved analogously to the cases described above. No oxidized product formed from N-acetylaziridine was detected, acid-catalyzed solvolysis being the predominant reaction. The presence of a strongly

acidic region in the close vicinity of the anode has been suggested and the incompatibility of the highly strained aziridine system with acidic conditions is known, both of which are elements that could explain the outcome of the reaction. N-Formylazetidine disclosed a somewhat different behaviour, in that solvolysis took place after the formation of the oxidation product, reflecting the lower strain in four-membered rings. Attempts to thwart acid-catalyzed side-reactions were unsuccessful. (Paper IV.)

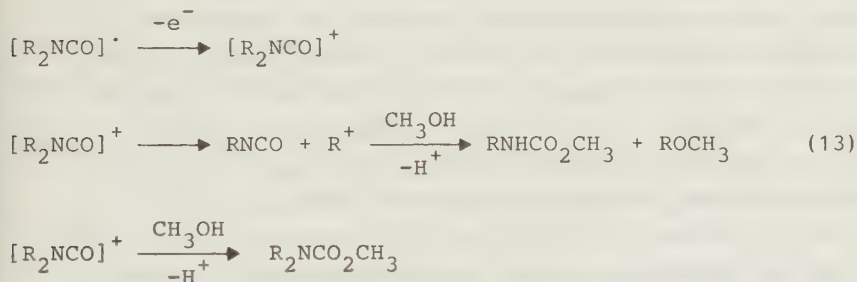
3.3 Anodic oxidation of N,N-di-tert-butylformamide and N-formyl-2,2,6,6-tetramethylpiperidine

The results presented in Paper IV and discussed above in a way represent natural border-line cases in the alkoxylation of heterocyclic amides. Such border-line cases, either encountered incidentally or by deliberate molecule design, often provide information otherwise obscured by mainstream reaction paths. To be able to disclose an odd but nevertheless possible route it is sometimes necessary to exaggerate a certain structural feature. During the exploitation of amide oxidations a number of cases were found where no product was formed³¹ (or where product formation was extraordinarily slow) in spite of expectations based on previous findings. A possible explanation was a substrate regenerating process involving the formyl hydrogen (eqn. 12). To unambiguously establish the validity of



a mechanism as suggested in eqn. 12 it was essential to study an amide without N- α hydrogens, the presence of which would otherwise bring about a "normal" reaction, trusting that continuous formation of the intermediate radical would enable competitive reactions to interfere. N,N-di-tert-Butylformamide, and N-formyl-2,2,6,6-tetramethylpiperidine which represents an alicyclic analogue, are fully substituted at the N- α carbons but nevertheless are ordinary aliphatic amides, offered this

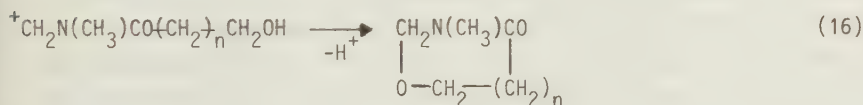
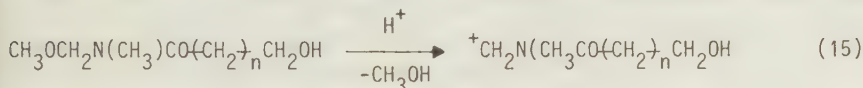
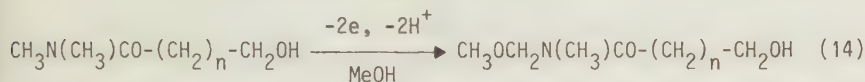
quality. Paper V summarizes the results obtained from anodic oxidation of these two compounds. Both proved to be difficult to oxidize, *i.e.* product formation was slow, and required the passage of large amounts of current to allow for reliable product analysis. However, product formation and subsequent analysis were successful and clearly substantiated the formation of methyl N-tert-butylcarbamate and N-methoxycarbonyl-2,2,6,6-tetramethylpiperidine. The composition of the products was indicative of the involvement of the regenerating process proposed and could be rationalized as follows: The radical formed after deprotonation of the radical cation is further oxidized to a cation. Depending on the structure of the parent amide the cation could either expel a cationic species, *i.e.* tert-butyl cation, and the isocyanate so formed react with the solvent, or, when sterical requirements allow, react directly with the solvent (eqn. 13). This diversification in product structure is presumably dependent on differing sterical demands in the parent amides.



3.4 Methoxylation of ω -hydroxyalkyl-N,N-dimethylcarboxamides

The history of anodic substitution could be described as the history of intermolecular reactions. Over the years electrochemists have dedicated themselves to the exploitation and elucidation of substitution reactions involving the employment of external nucleophiles. These could be the usual kinds such as methoxide, acetate or water, or carbon nucleophiles promoting coupling reactions (see eqn. 1). In spite of the synthetic possibilities apparent, very few reports concerning

the use of methanol as solvent in the ensuing experiments. The idea that cyclization should be favoured for kinetic reasons was, however, discredited by experimental evidence: On oxidation in methanol the only product derived from 3-hydroxy-N,N-dimethylpropanamide was the "normal" methoxylation product 3-hydroxy-N-methoxymethylene-N-methylpropanamide (eqn. 14, n = 1). The strangeness of this result was further highlighted



by the instantaneous cyclization of the latter to N-methyl-4-oxo-tetrahydro-1,3-oxazine upon acid treatment (eqns. 15 and 16, n = 1). This latter reaction can be regarded as the homogeneous counterpart to direct anodic cyclization and its successful accomplishment is suggestive of discrepancies between the, as hitherto believed, common cationic intermediates (Fig.6, eqn 15).

Evidently cyclization as a direct consequence of anodic oxidation is obstructed. In order to explain this phenomenon two entirely different approaches can be emphasized: a) No cation is formed during anodic oxidation, i.e. the generally accepted amide alkoxylation mechanism (eqns 7 and 8) is incorrect, or b) a cation is formed but becomes unavailable to an internal nucleophile owing to the heterogeneous reaction conditions, i.e. anode surface adsorption phenomena must be taken into account. Both these assumptions can be criticized on the basis of a number of conflicting results; the intermediacy of acyl-immonium ions in electrochemical oxidation of amides (and the analogous carbamates) is an undisputed everyday experience to workers in the field, anode surface adsorption interpretations, due to inconsistencies in experimental results, fell into disrepute in the mid-seventies.⁴⁸ Nevertheless a few

pro's can be formulated for each of these interpretations. Beside the findings related here the following cases where product composition cannot be fully rationalized by the intermediacy of a cation should be considered: N-Formyl-2-methylpiperidine on anodic oxidation provides a 95:5 ratio of substitution in the two positions available, the least substituted position, i.e. position 6, being the preferred site of attack.³¹ This is inconsistent with the prediction that an intermediate cation would preferentially be formed at the site of highest degree of alkyl substitution. This peculiarity is repeated in the open-chain analogue N-isopropyl-N-methylformamide³¹ and can be taken for granted in the results obtained by Mitzlaff et al.^{23d} and by Shono et al.^{43b} where they report exclusive formation of N-acetyl-2-methyl-6-methoxypiperidine and N-benzoyl-2-methyl-6-methoxypiperidine, and N-methoxycarbonyl-2-methyl-6-methoxypiperidine, respectively, from the appropriate precursors. Anodic methoxylation of N,N-diisopropylformamide is a remarkably slow process.^{23b} Complete conversion to the methoxy derivative requires the passage of 10-12 F/mol of substrate, suggesting that the intermediacy of a stabilized tertiary cation is not obvious. Furthermore, N,N-dibenzylformamide does not give any detectable products on attempted anodic methoxylation in spite of the benzylic activation.⁴⁹ These findings are discrepant with elementary expectations based on carbocation reactivity/formation theory thus implying that the actual mechanism might involve components yet unrecognized.

Hypotheses involving surface adsorption can be characterized as essentially ad hoc. Present state-of-the-art methodology does not lend itself to an unequivocal estimate of the actual impact of surface adsorption upon a given electrochemical reaction. This leaves discussions to be based mainly on comparison between molecules of different sterical demand. Although reported anodically promoted cyclizations are few, the amides/carbamates used have a common denominator in that the internal nucleophile is located at the nitrogen side of the molecule. If then the assumption is made that the amide oxygen is adsorbed to the anode surface, the nitrogen-alkyl moiety would reach out into the solution where the internal nucleophile would be able to successfully compete for the intermediate cation^{48a,45}

(Fig. 7). For the ω -hydroxyalkane-N,N-dimethylcarboxamides the situation would be the opposite. The internal nucleophile, now

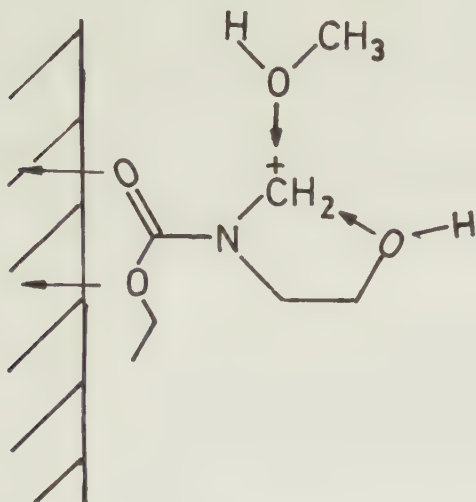


Fig. 7

located at the carbonyl side of the molecule would probably be as firmly adsorbed to the anode as the amide oxygen, thus being

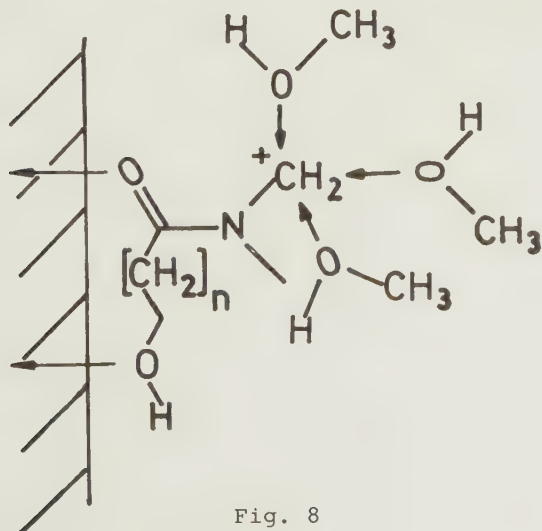


Fig. 8

completely deprived of opportunities to engage in competitive reactions (Fig. 8).

In order to avoid singularities due to structural features, hydroxyamide precursors to five-, seven-, eight- and nin-membered rings were examined analogously. The outcome of these experiments emphasized the previously encountered reluctance to engage in direct cyclization. No cyclized products were formed but only N- α methoxylation was observed (eqn. 14, $n = 0, 2, 3, 4$). Cyclization was feasible, in favourable cases, when treating the methoxylated amides with the appropriate acid in homogeneous solution (eqns. 15 and 16, $n = 0, 2$).

ACKNOWLEDGEMENTS

I would like to express my gratitude to Professor Lennart Eberson and Docent Klas Nyberg for their countenance throughout this work.

The following members of the technical staff are hereby acknowledged:

Mrs. Heleen Hjalmarsson for dexterous typing.

Messrs. Jan Glans, Einar Nilsson and Rolf Servin for expert spectral recordings.

Messrs. Ove Anderberg and Lars Tregge for skilfull technical assistance.

Thanks are due to the members of the NMR group for valuable assistance with spectral interpretations. I am also indebted to Docent Peter Sellers for linguistic criticism.

Finally, I would like to acknowledge my appreciation of the support and help given by my colleagues and friends at the Chemical Center.

Financial support by the Swedish Natural Science Research Council and the Royal Physiographic Society in Lund is gratefully acknowledged.

4. REFERENCES

1. Adams, R.N. Electrochemistry at Solid Electrodes, Dekker New York (1969).
2. Mann, C.K. and Barnes, K.K. Electrochemical Reactions in Nonaqueous Systems, Dekker, New York (1970).
3. Baizer, M.M., Ed. Organic Electrochemistry, Dekker, New York (1973).
4. Meites, L. and Zuman, P. Handbook of Organic Electrochemistry, Blackwell Scientific, Oxford (1978).
5. Ebersson, L. and Nyberg, K. Accounts Chem. Res. 6 (1973)
6. Ebersson, L. and Nyberg, K. Adv. Phys. Org. Chem. 12 (1976) 1.
7. Ebersson, L. in Modern Synthetic Methods, Vol. 2, Scheffold, R. Ed., Salle Verlag and Verlag Sauerländer (1980).
8. Weinberg, N.L., Ed. Technique of Electroorganic Synthesis Parts I and II, Wiley, New York (1974 and 1975).
9. Ross, S.D., Finkelstein, M. and Rudd, E.J. Anodic Oxidation, Academic Press, New York (1975).
10. Bard, A.J. and Lund, H. Encyclopedia of Electrochemistry of the Elements, Vol. XI, Dekker, New York (1978).
11. Ebersson, L. and Schäfer, H. Fortschr. Chem. Forsch. 21 (1971) 1.
12. Ebersson, L. and Nyberg, K. Tetrahedron 32 (1976) 2185.
13. a. Linstead, R.P., Bunt, J.C., Weedon, B.C.L. and Shephard, B.R. J. Chem. Soc. (1952) 3624; b. Wilson, C.L. and Lippincott, W.T. J. Am. Chem. Soc. 78 (1956) 4291; c. Ebersson, L. and Nyberg, K. ibid. 88 (1966) 1686; d. For a review, see Ref. 5.
14. Ebersson, L. Acta Chem. Scand. 17 (1963) 2004.
15. Ebersson, L. In Organic Electrochemistry, Baizer, M.M., Ed. Dekker, New York (1973). Chapter XII.
16. Ebersson, L. Acta Chem. Scand. B 34 (1980) 747.
17. Ebersson, L. J. Am. Chem. Soc. 89 (1967) 4669.
18. Cf. Ref. 13c.
19. Ross, S.D., Finkelstein, M. and Petersen, R.C. J. Org. Chem. 35 (1970) 781.
20. Magnusson, C., Olofsson, B. and Nyberg, K. Chem. Scripta

1 (1971) 57.

21. Petit, G. and Bessi re, J. J. Electroanal. Chem. 31 (1971) 393.
22. a. Hubert, J.C., Steege, W., Speckamp, W.N. and Huisman, H.O. Synth. Commun. 1 (1971) 103; b. Dijkink, J. and Speckamp, W.N. Tetrahedron 34 (1978) 173; c. Schoemaker, H.E. and Speckamp, W.N. Tetrahedron Lett. (1978) 1515.
23. a. Rudd, E.J., Finkelstein, M. and Ross, S.D. J. Org. Chem. 37 (1972) 1763; b. Nyberg, K. and Servin, R. Acta Chem. Scand. B 30 (1976) 640; c. Nyberg, K., Malmberg, M. and Servin, R. AIChE Symposium Series No 185, 75 (1979) 36; d. Mitzlaff, M., Warning, K. and Jensen, M. Justus Liebigs Ann. Chem. (1978) 1713; Cf. Ger. Offen. No 2.113.338 (1972).
24. a. O'Donnell, J.F. and Mann, C.K. J. Electroanal. Chem. 13 (1967) 157; b. ibid. 13 (1967) 163.
25. Ross, S.D., Finkelstein, M. and Petersen, R.C. J. Am. Chem. Soc. 86 (1964) 4139.
26. a. Eberson, L., J nsson, L. and Wistrand, L.-G. Acta Chem. Scand. B 32 (1978) 520; b. Eberson, L. and Nyberg, K. ibid. B 32 (1978) 235; c. Cf. Ref. 9; d. Cf. Ref. 6.
27. a. Nyberg, K. and Wistrand, L.-G. J. Org. Chem. 43 (1978) 2613; b. Andrulis, P.J. Dewar, M.J.S., Dietz, R. and Hunt, R.L. J. Am. Chem. Soc. 88 (1966) 5473.
28. J nsson, L. and Wistrand, L.-G. J. Chem. Soc. Perkin Trans. 1 (1979) 669.
29. Eberson, L. and Webber, A. Acta Chem. Scand. B In press.
30. Berti, G. J. Org. Chem. 22 (1957) 230.
31. Blum, Z. Unpublished results.
32. Eberson, L. J. Am. Chem. Soc. 89 (1967) 4669.
33. a. Clark, D.B., Fleischmann, M. and Pletcher, D. J. Chem. Soc. Perkin 2 (1973) 1587; b. Kochi, J.K., Tang, R.T. and Bernath, T. J. Am. Chem. Soc. 95 (1973) 7114.
34. a. So, Y-H., Becker, J.Y. and Miller, L.L. J. Chem. Soc. Chem. Commun. (1975) 262; b. So, Y-H. and Miller, L.L. Synthesis (1976) 468.
35. Weinberg, N.L. and Wu, C.N. Tetrahedron Lett. 39 (1975) 3367.

36. Bockmair, G., Fritz, H.P. and Gebauer, H. Electrochim. Acta 23 (1978) 29.
37. Wistrand, L.-G. Ph.D. Thesis, Lund 1978.
38. Fritz, H.P. and Kremer, H.-J. Z. Naturforsch. 31b (1976) 1565.
39. Nyberg, K. and Wistrand, L.-G. J. Chem. Soc. Chem. Commun. (1976) 898.
40. Eberson, L. and Jönsson, L. J. Chem. Soc. Chem. Commun. (1980) 1187; ibid. (1981) 133.
41. Ross, S.D., Finkelstein, M. and Petersen, R.C. J. Am. Chem. Soc. 88 (1966) 4657 and references cited therein.
42. Eberson, L., Nyberg, K. and Sternerup, H. Chem. Scripta 3 (1973) 12.
43. a. Shono, T., Hamaguchi, M. and Matsumura, Y. J. Am. Chem. Soc. 97 (1975) 4264; b. Shono, T., Matsumura, Y. and Tsubata, K. ibid. 103 (1981) 1172.
44. a. Malmberg, M. and Nyberg, K. Acta Chem. Scand. B 33 (1979) 69; b. ibid. B 35 (1981) 411.
45. Irie, K., Okita, M., Wakamatsu, T. and Ban, Y. Nouveau J. Chimie 4 (1980) 275.
46. Tabakovic, I., Trkovnik, M. and Galijas, D. J. Electroanal. Chem. 86 (1978) 241.
47. Weinberg, N.L. and Brown, E.A. J. Org. Chem. 31 (1966) 4058.
48. For a discussion, see Dirlam, J., Eberson, L. and Sternerup, H. Chem.-Ing. Tech. 44 (1972) 178 and references cited therein.
49. Malmberg, M. Personal communication.

